FORM PTO-1390 (Modified) (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR
1751	09/913555

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/DE 00/00444	FEBRUARY 11, 2000	FEBRUARY 20, 1999

TITLE OF INVENTION

BIODEGRADABLE, INJECTABLE OLIGOMER-POLYMER COMPOSITION

APPLICANT(S) FOR DO/EO/US

Cristoph VOELKEL, Manuela PFEIFFER, Sabine FRICKE, Sebastian VOGT, Ernst-Joachim BORMANN, Matthias SCHNABELRAUCH, Birgitt BEER

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ A copy of the International Search Report (PCT/ISA/210).
8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 18 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
    A **SECOND** or **SUBSEQUENT** preliminary amendment.
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☒ Certificate of Mailing by Express Mail
19. ☐ Other items or information:

EL364015584 US

518 Rec'd PCT/PTO 15 AUG 2001

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/913555	PCT/DE 00/00444	1751

20. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐	Search Report has been prepared by the EPO or JPO	**$930.00**
☐	International preliminary examination fee paid to USPTO (37 CFR 1.482)	**$720.00**
☐	No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))	**$790.00**
☒	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO	**$1,070.00**
☐	International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	**$98.00**

ENTER APPROPRIATE BASIC FEE AMOUNT =	**$1,000.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	13 - 20 =	0	x $18.00	**$0.00**	
Independent claims	1 - 3 =	0	x $80.00	**$0.00**	
Multiple Dependent Claims **(check if applicable).**			☐	**$0.00**	
TOTAL OF ABOVE CALCULATIONS =				**$1,000.00**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable).** ☐				**$0.00**	
SUBTOTAL =				**$1,000.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				**$0.00**	
TOTAL NATIONAL FEE =				**$1,000.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				**$0.00**	
TOTAL FEES ENCLOSED =				**$1,000.00**	
				Amount to be: refunded	$
				charged	$

☐ A check in the amount of to cover the above fees is enclosed.

☒ Please charge my Deposit Account No. **19-4675** in the amount of **$1,000.00** to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **19-4675** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

STRIKER, STRIKER & STENBY
103 EAST NECK ROAD
HUNTINGTON, NEW YORK 11743

SIGNATURE

MICHAEL J. STRIKER
NAME

27233
REGISTRATION NUMBER

AUGUST 15, 2001
DATE

UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: Group: Attorney Docket # 1751

Applicant(s) : VOELKEL, C., ET AL

Serial No. :

Filed :

For : BIODEGRADABLE, INJECTABLE OLIGOMER-POLYMER COMPOSITION

SIMULTANEOUS AMENDMENT

August 13, 2001

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

S I R S:

Simultaneously with filing of the above identified application please amend the same as follows:

In the Claims:

Cancel all claims without prejudice.

Substitute the claims attached hereto.

REMARKS:

This Amendment is submitted simultaneously with filing of the above identified application.

With the present Amendment applicant has amended the claims so as to eliminate their multiple dependency.

Consideration and allowance of the present application is most respectfully requested.

Respectfully submitted,

Michael J. Striker
Attorney for Applicant(s)
Reg. No. 27233

Patentansprüche

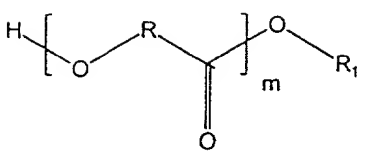
1. Oligomer-Polymer-Zusammensetzung bestehend aus einer Kombination von mindestens zwei biologisch abbaubaren Hilfsstoffen und mindestens einem biologisch aktiven Wirkstoff.

2. Oligomer-Polymer-Zusammensetzung gemäß Anspruch 1, dadurch gekennzeichnet, daß die biologisch abbaubaren Hilfsstoffe Polymerisationsprodukte von gleichen oder unterschiedlichen Hydroxycarbonsäuren sind.

3. Oligomer-Polymer-Zusammensetzung gemäß Anspruch 2, dadurch gekennzeichnet, daß die Hydroxycarbonsäuren Milchsäure oder Glycolsäure sind.

4. Oligomer-Polymer-Zusammensetzung gemäß einem der vorangehenden Ansprüche, dadurch gekennzeichnet, daß jeweils mindestens einer der biologisch abbaubaren Hilfsstoffe ein flüssiges niedermolekulares Oligomer und der andere ein festes höhermolekulares Polymer ist.

5. Oligomer-Polymer-Zusammensetzung gemäß Anspruch 4, dadurch gekennzeichnet, daß das flüssige niedermolekulare Oligomer eine Verbindung der allgemeinen Formel I, II oder III



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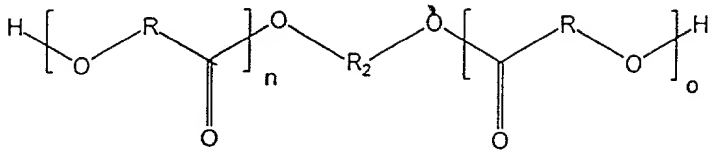

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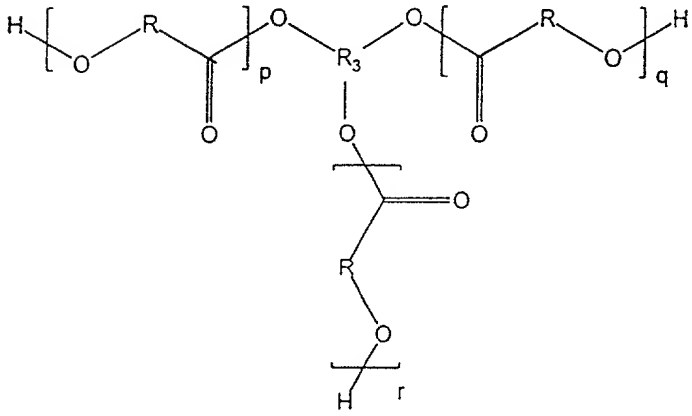


II

ist, worin

R für die Variablen m, n, o ,p, q und r jeweils gleich oder unterschiedlich ist und für $-CH_2-$, $-CH(CH_3)-$, $-(CH_2)_5-$, $-CH_2-CH_2-O-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-$ oder deren Homologe mit jeweils bis zu 5 weiteren C-Atomen steht,

R_1 für $-CH_2-COOY$, $-CH(CH_3)-COOY$, $-CH_2-CH_2-COOY$, $-CH_2-CH_2-CH_2-COOY$, $-CH_2-CH_2-CH_2-CH_2-COOY$, $-CH_2-CH_2-CH_2-CH_2-CH_2-COOY$, $-CH_2-CH(CH_3)-Y$, $-(cyclo-C_6H_{11})$ oder $-CH_2-C_6H_5-$ steht,

R_2 für $-CH_2-CH(CH_3)-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-CH_2-$, $-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$, $-CH_2-CH(-Y)-CH_2-$, cyclohexan-1,2-diyl, cyclohexan-1,3-diyl oder cyclohexan-1,4-diyl steht,

R_3 für $(-CH_2)_2CH-$, $(-CH_2)_3C-CH_3$ oder $(-CH_2)_3C-CH_2-CH_3$ steht,

wobei Y =-H, $-CH_3$, $-C_2H_5$, $-C_3H_7$ oder $-C_4H_9$ ist und

m, n, o, p, q und r unabhängig voneinander eine ganze Zahl von 2 bis 18 bedeuten.

6. Oligomer-Polymer-Zusammensetzung gemäß Anspruch 5, dadurch gekennzeichnet, daß R $-CH(CH_3)-$, R_1 $-CH(CH_3)-COOY$, mit Y = $-C_2H_5$, m, n, o, p, q oder r eine ganze Zahl von 2 bis 4 bedeuten.

7. Oligomer-Polymer-Zusammensetzung gemäß Anspruch 4, dadurch gekennzeichnet, daß das flüssige niedermolekulare Oligomer aus der folgenden Gruppe oder aus deren Mischungen ausgewählt ist, nämlich Poly(hydroxyester) wie Poly-(L-lactid)e, Poly-(D,L-lactid)e, Polyglycolide, Poly-(caprolacton)e, Poly-(dioxanon)e, Poly-(hydroxybutter-säure)n, Poly-(hydroxyvaleriansäure)n, Poly-(glycosalicylat)e und Copolymere dieser Verbindungen, Poly-(hydroxyester), die durch Ringöffnungspolymerisation von Lactonen in Gegenwart eines biokompatiblen Startmoleküls herstellbar sind, nämlich L-Lactid, D,L-Lactid, Glycolid, p-Dioxanon und e-Caprolacton, mit aliphatischen oder cycloaliphatischen Verbindungen mit einer oder mehreren freie Hydroxylgruppen wie L-Milchsäure-

alkylester, Cholesterol, Propan-1,2-diol, Triethylenglykol, Glycerol oder Pentaerythrit als biokompatible Startmoleküle.

8. Oligomer-Polymer-Zusammensetzung nach einem der Ansprüche 4 bis 7, dadurch gekennzeichnet, daß das Verhältnis zwischen den festen höhermolekularen Polymeren und den flüssigen niedermolekularen Oligomeren 1:100 bis 1:1, vorzugsweise 1:10 bis 1:2 beträgt.

9. Oligomer-Polymer-Zusammensetzung gemäß einem der voranstehenden Ansprüche, dadurch gekennzeichnet, daß der biologisch aktive Wirkstoff aus der Gruppe der Hormone, Immunmodulatoren, Immunsuppressiva, Antibiotika, Zytostatika, Diuretika, Magen-Darm-Mittel, Herz-Kreislauf-Mittel und Neuropharmaka ausgewählt ist.

10. Oligomer-Polymer-Zusammensetzung gemäß Anspruch 9, dadurch gekennzeichnet, daß der biologisch aktive Wirkstoff in der Hilfsstoffzusammensetzung in gelöster oder suspendierter Form vorliegt.

11. Oligomer-Polymer-Zusammensetzung gemäß einem der voranstehenden Ansprüche, dadurch gekennzeichnet, daß diese in Form eines injizierbaren Mittels vorliegt, welches nach Injektion unter dem Einfluß der Körperflüssigkeit eine Koagulat bildet.

12. Injizierbares Implantat, erhältlich durch Injektion einer Oligomer-Polymer-Zusammensetzung gemäß Anspruch 1 in einen Körper.

13. Verfahren zur Herstellung eines injizierbaren Implantats, dadurch gekennzeichnet, daß man eine Oligomer-

Polymer-Zusammensetzung nach Anspruch 1 in einen Körper eines Säugers injiziert.

Patentansprüche

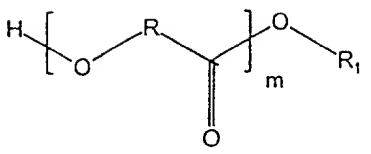
1. Oligomer-Polymer-Zusammensetzung bestehend aus einer Kombination von mindestens zwei biologisch abbaubaren Hilfsstoffen und mindestens einem biologisch aktiven Wirkstoff.

2. Oligomer-Polymer-Zusammensetzung gemäß Anspruch 1, dadurch gekennzeichnet, daß die biologisch abbaubaren Hilfsstoffe Polymerisationsprodukte von gleichen oder unterschiedlichen Hydroxycarbonsäuren sind.

3. Oligomer-Polymer-Zusammensetzung gemäß Anspruch 2, dadurch gekennzeichnet, daß die Hydroxycarbonsäuren Milchsäure oder Glycolsäure sind.

4. Oligomer-Polymer-Zusammensetzung gemäß Anspruch 1, he, dadurch gekennzeichnet, daß jeweils mindestens einer der biologisch abbaubaren Hilfsstoffe ein flüssiges niedermolekulares Oligomer und der andere ein festes höhermolekulares Polymer ist.

5. Oligomer-Polymer-Zusammensetzung gemäß Anspruch 4, dadurch gekennzeichnet, daß das flüssige niedermolekulare Oligomer eine Verbindung der allgemeinen Formel I, II oder III



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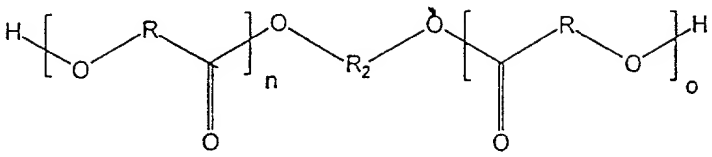

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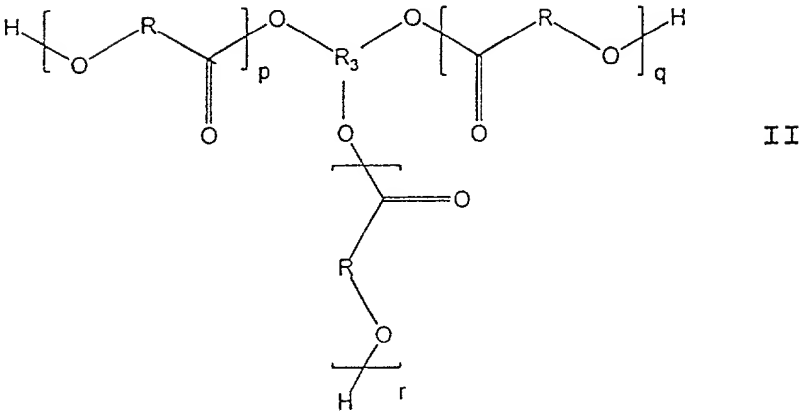

II

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R für die Variablen m, n, o ,p, q und r jeweils gleich oder unterschiedlich ist und für $-CH_2-$, $-CH(CH_3)-$, $-(CH_2)_5-$, $-CH_2-CH_2-O-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-$ oder deren Homologe mit jeweils bis zu 5 weiteren C-Atomen steht,

R_1 für $-CH_2-COOY$, $-CH(CH_3)-COOY$, $-CH_2-CH_2-COOY$, $-CH_2-CH_2-CH_2-COOY$, $-CH_2-CH_2-CH_2-CH_2-COOY$, $-CH_2-CH_2-CH_2-CH_2-CH_2-COOY$, $-CH_2-CH(CH_3)-Y$, $-(cyclo-C_6H_{11})$ oder $-CH_2-C_6H_5-$ steht,

R_2 für $-CH_2-CH(CH_3)-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-CH_2-$, $-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$, $-CH_2-CH(-Y)-CH_2-$, cyclohexan-1,2-diyl, cyclohexan-1,3-diyl oder cyclohexan-1,4-diyl steht,

R_3 für $(-CH_2)_2CH-$, $(-CH_2)_3C-CH_3$ oder $(-CH_2)_3C-CH_2-CH_3$ steht,

wobei Y =-H, $-CH_3$, $-C_2H_5$, $-C_3H_7$ oder $-C_4H_9$ ist und

m, n, o, p, q und r unabhängig voneinander eine ganze Zahl von 2 bis 18 bedeuten.

6. Oligomer-Polymer-Zusammensetzung gemäß Anspruch 5, dadurch gekennzeichnet, daß R $-CH(CH_3)-$, R_1 $-CH(CH_3)-COOY$, mit Y = $-C_2H_5$, m, n, o, p, q oder r eine ganze Zahl von 2 bis 4 bedeuten.

7. Oligomer-Polymer-Zusammensetzung gemäß Anspruch 4, dadurch gekennzeichnet, daß das flüssige niedermolekulare Oligomer aus der folgenden Gruppe oder aus deren Mischungen ausgewählt ist, nämlich Poly(hydroxyester) wie Poly-(L-lactid)e, Poly-(D,L-lactid)e, Polyglycolide, Poly-(caprolacton)e, Poly-(dioxanon)e, Poly-(hydroxybutter-säure)n, Poly-(hydroxyvaleriansäure)n, Poly-(glycosalicylat)e und Copolymere dieser Verbindungen, Poly-(hydroxyester), die durch Ringöffnungspolymerisation von Lactonen in Gegenwart eines biokompatiblen Startmoleküls herstellbar sind, nämlich L-Lactid, D,L-Lactid, Glycolid, p-Dioxanon und e-Caprolacton, mit aliphatischen oder cycloaliphatischen Verbindungen mit einer oder mehreren freie Hydroxylgruppen wie L-Milchsäure-

alkylester, Cholesterol, Propan-1,2-diol, Triethylenglykol, Glycerol oder Pentaerythrit als biokompatible Startmoleküle.

8. Oligomer-Polymer-Zusammensetzung nach Anspruch 4, dadurch gekennzeichnet, daß das Verhältnis zwischen den festen höhermolekularen Polymeren und den flüssigen niedermolekularen Oligomeren 1:100 bis 1:1, vorzugsweise 1:10 bis 1:2 beträgt.

9. Oligomer-Polymer-Zusammensetzung gemäß Anspruch 1, dadurch gekennzeichnet, daß der biologisch aktive Wirkstoff aus der Gruppe der Hormone, Immunmodulatoren, Immunsuppressiva, Antibiotika, Zytostatika, Diuretika, Magen-Darm-Mittel, Herz-Kreislauf-Mittel und Neuropharmaka ausgewählt ist.

10. Oligomer-Polymer-Zusammensetzung gemäß Anspruch 9, dadurch gekennzeichnet, daß der biologisch aktive Wirkstoff in der Hilfsstoffzusammensetzung in gelöster oder suspendierter Form vorliegt.

11. Oligomer-Polymer-Zusammensetzung gemäß Anspruch 1, dadurch gekennzeichnet, daß diese in Form eines injizierbaren Mittels vorliegt, welches nach Injektion unter dem Einfluß der Körperflüssigkeit eine Koagulat bildet.

12. Injizierbares Implantat, erhältlich durch Injektion einer Oligomer-Polymer-Zusammensetzung gemäß Anspruch 1 in einen Körper.

13. Verfahren zur Herstellung eines injizierbaren Implantats, dadurch gekennzeichnet, daß man eine Oligomer-

Polymer-Zusammensetzung nach Anspruch 1 in einen Körper eines Säugers injiziert.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: **Art Unit:** **Docket No.: 1751**

In RE: **U.S. National Stage Application of C. VOELKEL, et al**
crsp. to PCT/DE 00/00444

Ser. No: **09/913,555**

Filed: **August 15, 2001 (Mailroom receipt date)**

October 11, 2001

PRELIMINARY AMENDMENT

Box: PCT

Hon. Commissioner of Patents

and Trademarks,

Washington, D.C. 20231

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.
On 10/11/01

Sir:

In advance of Examination on the merits, please make the following changes and consider the following REMARKS:

In the Specification:

Page 1, between line 2 (title) and 3 (first paragraph), please insert the following:

BACKGROUND OF THE INVENTION

1. Field of the Invention --.

Page 1, between the first paragraph and the second paragraph, please insert the following heading:

2. Description of the Related Art .

Page 3, above line 1, please insert **SUMMARY OF THE INVENTION** .

Page 10, between next to last line and last line, please insert the following:

BRIEF DESCRIPTION OF THE DRAWING

The objects, features and advantages of the invention will now be illustrated in more detail with the aid of the following description of the preferred embodiments, with reference to the accompanying figures in which:

Figure 1 shows two release profiles of a biologically active ingredient, Cytochrome c, from two examples of the injectable implant composition according to the invention; and

Figure 2 shows two release profiles of two active ingredients, testosterone and testosterone unadeconate, from another example of the injectable implant composition according to the invention.

EXAMPLES

In the Drawing:

The original figs. 1 and 2 contained German wording. Please accept the replacement figures 1 and 2 with English wording attached to this amendment. Approval of the replacement figures is respectfully requested.

In the Abstract:

Please replace the original abstract with the following replacement abstract:

ABSTRACT OF THE DISCLOSURE

A biodegradable, injectable oligomer-polymer composition is described, which consists of a combination of at least two biologically degradable inert materials and at least one biologically active ingredient. The inventive, oligomer-polymer composition coagulates when injected into the body of a mammal and forms an implant, from which the biologically active ingredient is released. The rate of release can be adjusted by controlling the type and amount of the ingredients of the oligomer-polymer composition.

In the Claims:

Please cancel claims 1 to 13 without prejudice and add claims 14 to 28 as follows:

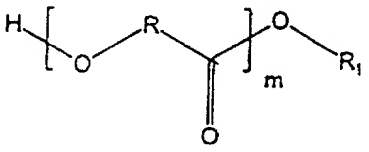
14. An injectable oligomer-polymer composition, consisting of a combination of at least two biologically degradable inert materials and at least one biologically active ingredient, and wherein at least one of the at least two biologically degradable inert materials comprises an oligomeric ester of at least one hydroxycarboxylic acid and at least one other of the at least two biologically degradable inert materials comprises a polymeric ester of at least one hydroxycarboxylic acid.

15. The oligomer-polymer composition as defined in claim 14, wherein the at least two biologically degradable inert materials are polymerization products of identical or different hydroxycarboxylic acids.

16. The oligomer-polymer composition as defined in claim 14, wherein each of the at least two biologically degradable inert materials is a different polymerization product of hydroxycarboxylic acid monomers and each of said hydroxycarboxylic acid monomers of each of said polymerization product is selected from the group consisting of lactic acid and glycolic acid.

17. The oligomer-polymer composition as defined in claim 14, wherein at least one of the at least two biologically degradable inert materials is a liquid oligomer and another of the at least two biologically degradable inert materials is a solid polymer, said solid polymer having a molecular weight that is greater than that of said liquid oligomer.

18. The oligomer-polymer composition as defined in claim 17, wherein the liquid oligomer is of formula I, II or III



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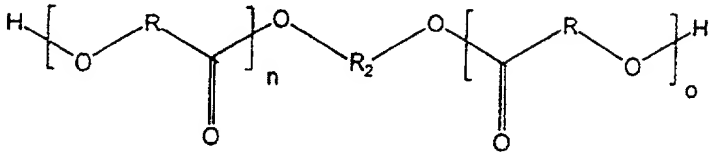

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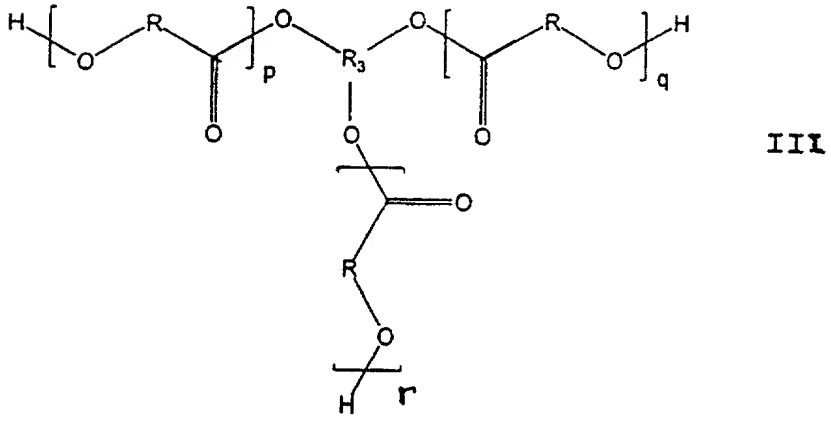


III

wherein R is the same or different in monomer units of the formula I, II or III that are identified by m, n, o, p, q and r and R represents

$-CH_2-$, $-CH(CH_3)-$, $-(CH_2)_5-$, $-CH_2-CH_2-O-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-$ or homologs thereof each with up to 5 further carbon atoms;

R_1 represents $-CH_2-COOY$, $-CH(CH_3)-COOY$, $-CH_2-CH_2-COOY$, $-CH_2-CH_2-CH_2COOY$, $-CH_2-CH_2-CH_2-CH_2-COOY$, $-CH_2-CH_2-CH_2-CH_2-CH_2-COOY$, $-CH_2CH(CH_3)-Y$, $-(\text{cyclo-}C_6H_{11})$ or $-CH_2-C_6H_5$;

R_2 represents $-CH_2-CH(CH_3)-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-CH_2-$, $-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$, $-CH_2-CH(-Y)-CH_2-$, cyclohexane-1,2-diyl, cyclohexane-1,3-diyl or cyclohexane-1,4-diyl;

R_3 represents $(-CH_2)_2CH-$, $(-CH_2)_3-CH_3$ or $(-CH_2)_3C-CH_2-CH_3$;

Y represents -H, $-CH_3$, $-C_2H_5$, $-C_3H_7$ or $-C_4H_9$, and

wherein m, n, o, p, q and r, independently of one another, are each a whole number from 2 to 18.

19. The oligomer-polymer composition as defined in claim 18, wherein said R is said $-CH(CH_3)-$, said R_1 is said $-CH(CH_3)-COOY$, said Y is said $-C_2H_5$ and said m, n, o, p, q or r is an integer from 2 to 4.

20. The oligomer-polymer composition as defined in claim 17, wherein the liquid oligomer is selected from the group consisting of poly-(L-lactides), poly-(D,L-

lactides), polyglycolides, poly-(caprolactones), poly(dioxanones), poly-(hydroxybutyric acids), poly-(hydroxyvaleric acids) and poly-(glycosalicylates), or mixtures thereof, or copolymers thereof made by a process comprising ring opening polymerization of lactones in the presence of a biocompatible starter molecule, and wherein said lactones are selected from the group consisting of L-lactide, D,L-lactide, glycolide, p-dioxanone and e-caprolactone and said biocompatible starter molecule is an aliphatic or cycloaliphatic compound with one or more free hydroxyl groups.

21. The oligomer-polymer composition as defined in claim 20, wherein said biocompatible starter molecule is an alkyl L-lactate, cholesterol, 1,2-dihydroxy-propane, triethyleneglycol, glycerol or pentaerythritol.

22. The oligomer-polymer composition as defined in claim 17, wherein the solid polymer and the liquid oligomer are present in a ratio of said solid polymer to said liquid oligomer of 1:100 to 1:1.

23. The oligomer-polymer composition as defined in claim 22, wherein said ratio is from 1:10 to 1:2.

24. The oligomer-polymer composition as defined in claim 14, wherein the biologically active ingredient is selected from the group consisting of hormones, immune modulators, immune suppressive agents, antibiotics, cytostatic agents,

diuretics, gastrointestinal drugs, cardiovascular drugs and neuropharmacological drugs.

25. The oligomer-polymer composition as defined in claim 24, wherein the biologically active ingredient is present in dissolved or suspended form in the inert materials.

26. The oligomer-polymer composition as defined in claim 14, in the form of an injectable material, which, when injected, forms a coagulate under the influence of body fluid.

27. An injectable implant, obtainable by injecting an oligomer-polymer composition into a body, wherein said oligomer-polymer composition comprises a combination of at least two biologically degradable inert materials and at least one biologically active ingredient, and wherein at least one of the at least two biologically degradable inert materials comprises an oligomeric ester of at least one hydroxycarboxylic acid and at least one other of the at least two biologically degradable inert materials comprises a polymeric ester of hydroxycarboxylic acids.

28. An injectable implant, obtainable by injecting an oligomer-polymer composition into a body, wherein said oligomer-polymer composition comprises

a liquid biodegradable oligomeric ester of at least one hydrocarboxylic acid and a solid biodegradable polymeric ester of at least one hydrocarboxylic acid, said solid biodegradable polymer having a molecular weight that is greater than that of said liquid biodegradable oligomer.

REMARKS

This is a preliminary amendment of the English translation of the specification, claims and abstract of the U.S. National Stage Application corresponding to **PCT/DE 00/00444.**

All the original claims 1 to 13 filed in the U.S. have been canceled and have been replaced by new claims 14 to 28. New claims 14 to 28 include the subject matter of the amended claims of October 18, 2000 in the International Application. However claims 14 to 28 have been drafted to better conform to the rules for claims in U.S. Patent Practice, while still describing the same invention as in the amended claims. Additional claims resulted because wording such as "especially" or "preferably" which results in claims of indefinite scope has not been used; instead additional dependent claims were drafted.

A replacement abstract was also provided and standard section headings recommend by U.S. Patent Office Rules were inserted in the specification.

Fig. 1 appeared to be missing and Fig. 2 had German wording on it. Please accept the accompanying replacement figures of Figs. 1 and 2, which have English wording. Approval of the changes in the drawings is respectfully requested.

APPENDIX SHOWING CHANGES IN THE ABSTRACT

Underlining shows additions; brackets show deletion

[Abstract of the Disclosure]**ABSTRACT OF THE DISCLOSURE**

A biodegradable, injectable oligomer-polymer composition is described, which consists of a combination of at least two biologically degradable inert materials and at least one biologically active ingredient. [

] The inventive, oligomer-polymer composition coagulates when injected into the body of a mammal and forms an implant, from which the biologically active ingredient is released. The rate of release can be adjusted by controlling the type and amount of the ingredients of the oligomer-polymer composition [selected].

Should the Examiner require or consider it advisable that the specification, claims and/or drawing be further amended or corrected in formal respects to put this case in condition for final allowance, then it is requested that such amendments or corrections be carried out by Examiner's Amendment and the case passed to issue. Any costs involved should be charged to the deposit account of the undersigned (No. 19-4675). Alternatively, should the Examiner feel that a personal discussion might be helpful in advancing the case to allowance, he or she is invited to telephone the undersigned at 1-631-549 4700.

In view of the foregoing, favorable allowance is respectfully solicited.

Respectfully submitted,

Michael J. Striker,

Attorney for the Applicants

Reg. No. 27,233

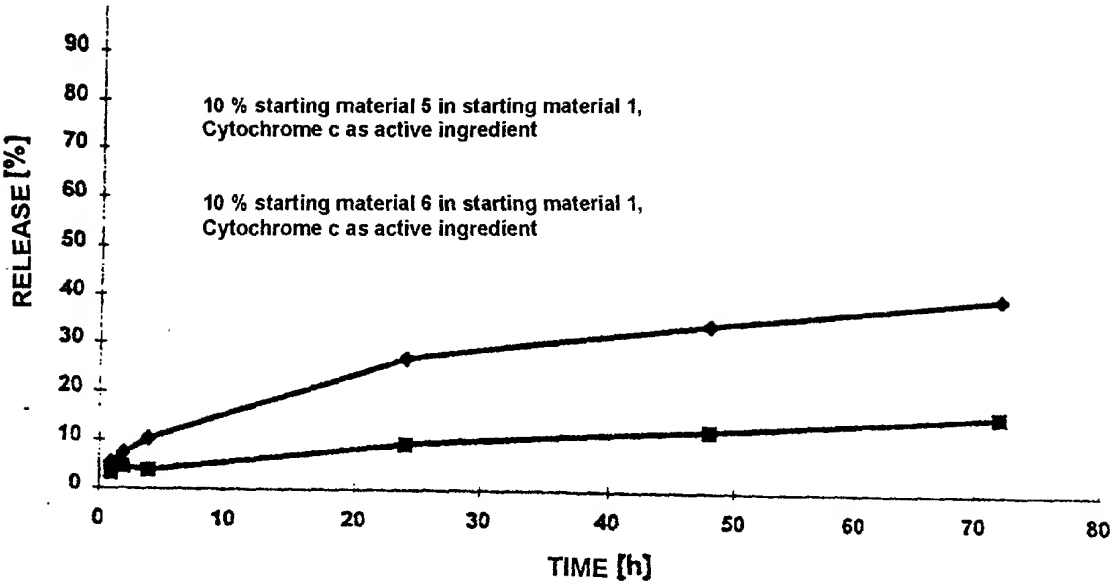


FIG. 1

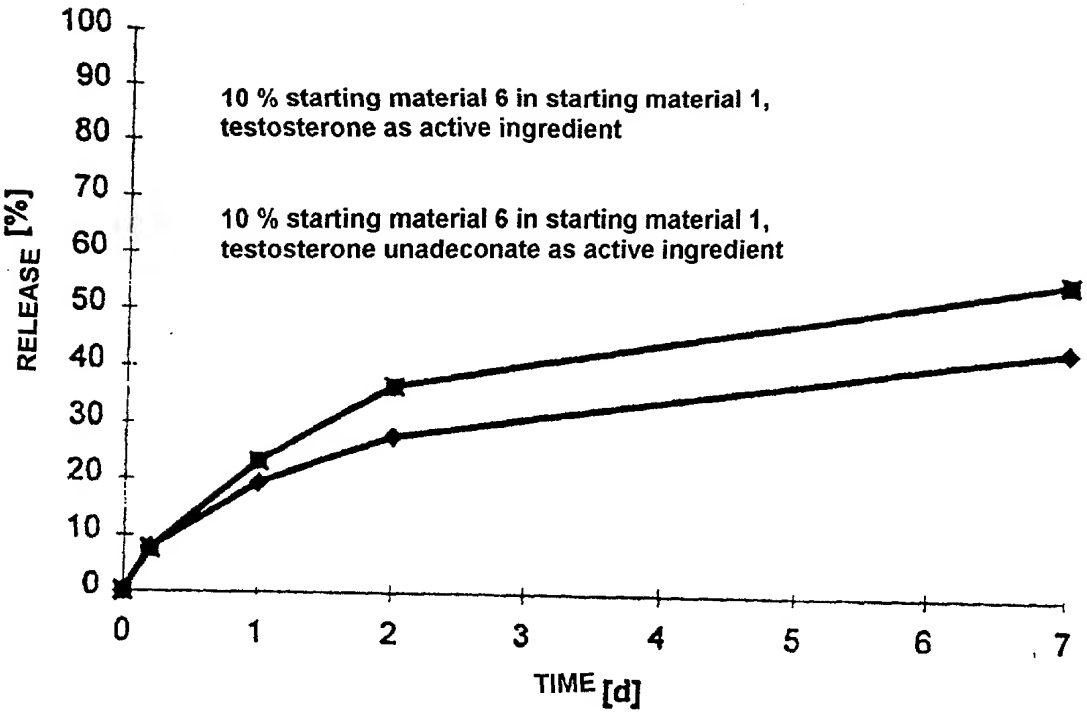

100
90
80
70
60
50
40
30
20
10
0
RELEASE [%]
10 % starting material 6 in starting material 1, testosterone as active ingredient
10 % starting material 6 in starting material 1, testosterone unadeconate as active ingredient
0
1
2
3
4
5
6
7
TIME [d]

FIG. 2

1751

BIODEGRADABLE, INJECTABLE OLIGOMER-POLYMER COMPOSITION

In the present invention relates to a biodegradable, injectable oligomer-polymer composition consisting of a combination of at least two biologically degradable inactive materials and at least one biologically active ingredient.

Implants for applying biologically active materials can be produced by compacting under aseptic conditions. These implants have the disadvantage that they are incapable of adapting to the spatial conditions of the site of the application and cause a sensation of pressure or pain there after the application.

A known solution to the problem of producing injectable implants furthermore consists of the use of microcapsules. The most common methods for producing microcapsules or microspheres are the so-called solvent evaporation technique, the spray-drying technique or the double emulsion technique. These methods require organic solvents or solvent mixtures such as dichloromethane, trichloromethane or a mixture of dichloromethane and methanol, which are toxic or at least physiologically hazardous for the living organism. The residual solvent content is therefore a common disadvantage of these methods. Moreover, the spray-drying method is associated with a relatively high expenditure for equipment.

Furthermore, the possibility exists of producing an implant in situ, when a solution or suspension of the biologically active material is applied parenterally. The in situ formation of an implant can be induced in various ways.

In the US patent 4,938,763, the biologically active substance is dissolved or dispersed in a solution of the biodegradable polymer, such as a

polylactide, and this solution or dispersion is injected. After the injection, a solid implant, consisting of the precipitated or coagulated biodegradable polymer and the biologically active substance, is formed on contact with the body fluid. The solvent migrates out of the implant and is distributed in the organism. It is a disadvantage of this method, that the solvents used, such as N-methyl-2-pyrrolidone, are physiologically active and therefore can be applied parenterally only to a slight extent, if at all.

Furthermore, in the patents cited, as well as in other patents (U.S. patents 5,278,201 and 5,278,202), liquid acrylate-terminated prepolymers, which can be synthesized, for example, by reacting poly(D,L-lactide-co-ε-caprolactone) with reactive acrylic acid derivatives, are proposed as in situ implant materials. The liquid prepolymer is injected in admixture with the biologically active substance and a suitable initiator, such as (dibenzoyl peroxide), which initiates the curing of the prepolymer and, with that, the formation of the implant in the body. The considerably higher synthesis and purification expenses for preparing the biologically degradable polymers and the parenteral administration of a physiologically hazardous, free radical-forming substance as initiator are disadvantages of this method. In addition, there has been no prior experience with the biocompatibility of said acrylate-terminated prepolymers or with the biodegradable of the implant formed form these substances.

In the US patent 5,702,717, the block copolymers of polyethylene glycol and polylactide or polycaprolactone are described, which, in aqueous solution at room temperature, are in the form of an injectable liquid and, at body temperature, form a gel, which contains the biologically active material. It is a disadvantage of this variation that the temperature for the transition from sol to gel depends on a plurality of different parameters, such as the composition and the degree of polymerization of the individual blocks in the block copolymer, the molecular weight of the block copolymer as well as the polymer concentration in the aqueous solution.

It is an object of the present invention to make available an oligomer-polymer composition as injectable implant, which overcomes the disadvantages of the state of the art.

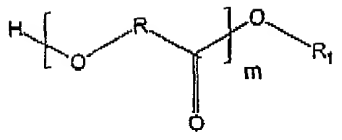
Pursuant to the invention, this objective is accomplished owing to the fact that an oligomer-polymer composition, consisting of a combination of at least two biologically degradable inert materials and at least one biologically active ingredient is made available.

Pursuant to the invention, the biologically degradable inert materials preferably are polymerization products of identical or different hydroxycarboxylic acids.

Lactic acid or glycolic acid are particularly preferred as hydroxycarboxylic acids.

It is furthermore preferred pursuant to the invention that in each case at least one of the biologically degradable inert materials is a liquid low molecular weight oligomer and the other a solid, higher molecular weight polymer.

Furthermore, it is preferred, pursuant to the invention, that the liquid, lower molecular weight oligomer is a compound of the general Formula I, II or III



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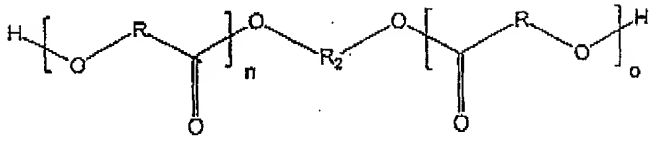

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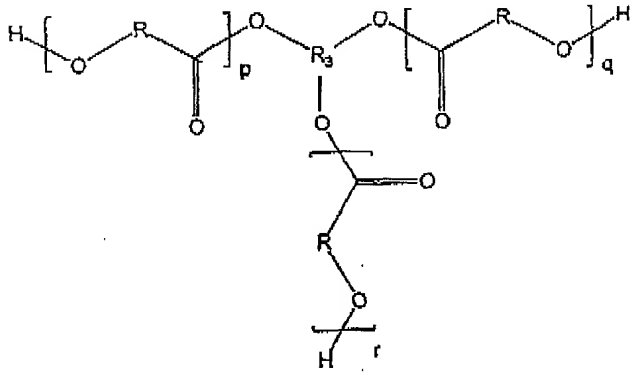


II

wherein

R is the same or different for the variables m, n, o, p, q and r and represents $-CH_2-$, $-CH(CH_3)-$, $-(CH_2)_5-$, $-CH_2-CH_2-O-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-0-CH_2-$ or their homologs with in each case up to 5 further carbon atoms,

R_1 represents $-CH_2-COOY$, $-CH(CH_3)-COOY$, $-CH_2-CH_2-COOY$, $-CH_2-CH_2-CH_2-COOY$, $-CH_2-CH_2-CH_2-CH_2-COOY$, $-CH_2-CH_2-CH_2-CH_2-CH_2-COOY$, $-CH_2-CH(CH_3)-Y$, $-(cyclo-C_6H_{11})$ or $-CH_2-C_6H_5$,

R_2 represents $-CH_2-CH(CH_3)-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-CH_2-$, $-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$, $-CH_2-CH(-Y)-CH_2-$, cyclohexane-1,2-diyl, cyclohexane-1,3-diyl or cyclohexane-1,4-diyl,

R_3 represents $(-CH_2)_2CH-$, $(-CH_2)_3-CH_3$ or $(-CH_2)_3C-CH_2-CH_3$,

Y being –H, $-CH_3$, C_2H_5, $-C_3H_7$ or $-C_4H_9$ and

m, n, o. p, q and r independently of one another being a whole number from 2 to 18.

It is especially preferred if R is $-CH(CH_3)-$, R_1 is $-CH(CH_3)-COOY$, Y is $-C_2H_5$ and m, n, o, p, q or r is a whole number from 2 to 4.

Therefore, for the synthesis of the implants, preferably poly(hydroxyesters), such as poly-(L-lactides), poly-(D,L-lactides), polyglycolides, poly-(caprolactones), poly(dioxanones), poly-(hydroxybutyric acids), poly-(hydroxyvaleric acids, poly-(glycosalicylates) and copolymers of these compounds are used. In particular, poly-(hydroxy esters), which are synthesized by a ring-opening polymerization of lactones in the presence of a biocompatible starter molecule, are preferred. Suitable lactones for carrying out the ring-opening polymerization preferably are, for example, L-lactide, D,L-lactide, glycolide, p-dioxanone and e-caprolactone. Suitable biocompatible starter molecules are preferably aliphatic or cycloaliphatic compounds, which contain one or more free hydroxyl groups. Particularly suitable starter molecules are, for example, alkyl esters of L-lactic acid, cholesterol, 1,2-dihydroxypropane, triethylene glycol, glycerol or pentaerythritol.

It is furthermore preferred that the ratio of solid higher molecular weight polymers to the liquid lower molecular weight oligomers is 1 : 100 to 1 : 1 and especially 1 : 10 to 1 : 2.

The inventive, pharmaceutical composition is furthermore characterized in that the biologically active ingredient is selected from the group comprising the hormones, immune modulators, immune suppressive agents, antibiotics, cytostatic agents, diuretics, gastrointestinal drugs, cardiovascular drugs, and neuropharmacological drugs.

Pursuant to the invention, the biologically active ingredient preferably is present in dissolved or suspended form in the combination of inert materials.

Pursuant to the invention, the pharmaceutical composition is in the form of an injectable agent which, after the injection, can form a coagulate under the influence of the body fluid.

Furthermore, an object of the present invention is an injectable implant, which is obtainable by injecting an inventive, pharmaceutical composition into a body.

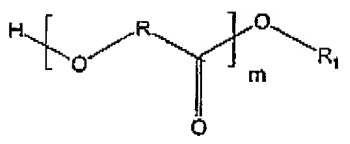
A further object of the invention is a method for the preparation of an injectable implant, wherein an inventive pharmaceutical composition is injected into the body of a mammal.

In other words, the object is accomplished pursuant to the invention owing to the fact that an in situ implant, which can be produced by placing a sterile, injectable composition of a biodegradable polymer, a biodegradable oligomer and the biologically active material in the organism and coagulating it under the influence of the body fluid, is made available.

The present invention accordingly relates to biologically degradable compositions of oligomeric and polymeric esters of hydroxycarboxylic acids, which can be produced by selecting suitable oligomeric and polymeric components as homogeneous solutions of adjustable viscosity or solids of low melting point without the use of further solvents or plasticizers. Said compositions of oligomers and polymers, after being injected into the human or animal organism, are capable of forming in situ coagulates under the influence of body fluid. The in situ implants, formed in this matter, can be used for the administration of biologically active materials in the organism.

During an investigation of a large number of biocompatible solvents or complexing agents, it was surprisingly found that biodegradable polymers, especially those of the group of polyhydroxy esters and their copolymers can be dissolved or converted into soluble complexes by oligomers of different hydroxycarboxylic acids with defined structures in a wide range of concentrations. These solutions or soluble complexes can be administered parenterally in a sterile form and, under the influence of body fluid, form coagulates in situ.

Furthermore, implants are preferred in which the biodegradable oligomer is a compound of the general Formula I, II or III



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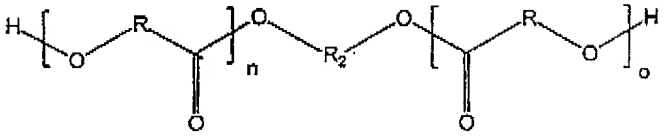

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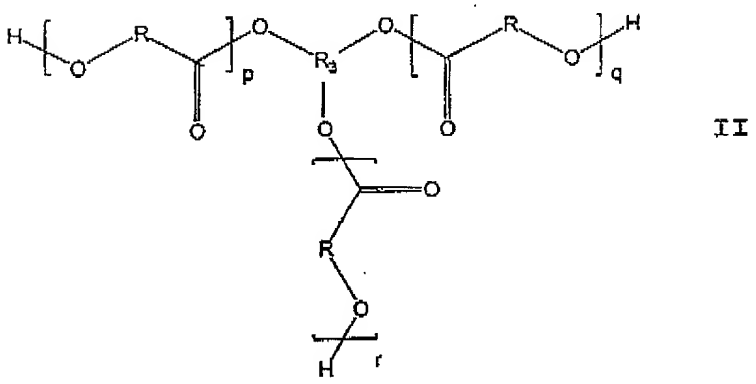


II

wherein

R is the same or different for the variables m, n, o, p, q and r and represents $-CH_2-$, $-CH(CH_3)-$, $-(CH_2)_5-$, $-CH_2-CH_2-O-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-0-CH_2-$ or their homologs with in each case up to 5 further carbon atoms,

R_1 represents $-CH_2-COOY$, $-CH(CH_3)-COOY$, $-CH_2-CH_2-COOY$, $-CH_2-CH_2-CH_2-COOY$, $-CH_2-CH_2-CH_2-CH_2-COOY$, $-CH_2-CH_2-CH_2-CH_2-CH_2-COOY$, $-CH_2-CH(CH_3)-Y$, $-(cyclo-C_6H_{11})$ or $-CH_2-C_6H_5$,

R_2 represents $-CH_2-CH(CH_3)-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-CH_2-$, $-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$, $-CH_2-CH(-Y)-CH_2-$, cyclohexane-1,2-diyl, cyclohexane-1,3-diyl or cyclohexane-1,4-diyl,

R_3 represents $(-CH_2)_2CH-$, $(-CH_2)_3-CH_3$ or $(-CH_2)_3C-CH_2-CH_3$,

Y being $-H$, $-CH_3$, $-C_2H_5$, $-C_3H_7$ or $-C_4H_9$ and

m, n, o, p, q and r independently of one another being a whole number from 2 to 18.

It is especially preferred if R is $-CH(CH_3)-$, R_1 is $-CH(CH_3)-COOY$, Y is $-C_2H_5$ and m, n, o, p, q or r is a whole number from 2 to 4.

Preferred implants have a ratio of biodegradable polymers to oligomer of 1 : 100 to 1 : 1 and especially 1 : 6 to 1 : 2.

The inventive compositions accordingly contain the above-mentioned biocompatible, biodegradable polymers and oligomers and are used without additional solvents or catalysts.

The inventive compositions may contain biologically active materials. In preferred implants, the coagulate contains at least one biologically active material, for example, from the group comprising hormones, immune modulators, immune suppressive agents, antibiotics, cytostatic agents, diuretics, gastrointestinal drugs,

cardiovascular drugs, anti-inflammatory agents, analgesics, local anesthetics and neuropharmacological drugs.

The inventive compositions are flowable in that they can be injected largely without causing pain. They can be subjected to the conventional sterilization methods.

After the inventive compositions, containing the biologically active substance, are placed in the organism, a coagulate is formed under the influence of the body fluid. As this coagulate is decomposed biologically in a process, which make take place over a period lasting formed weeks or months to years depending on the composition of the composition, the biologically active substance is released.

It is therefore preferred that the release of the biologically active substance be controlled by the components of the sterile, injectable composition and their relationship to one another. In this way, it is possible to adapt the rate of release to the pharmacokinetic and pharmacodynamic properties of the active ingredients in the organism.

The object of the present invention furthermore is a method for preparing and implant, wherein, pursuant to the invention, a sterile, injectable composition of a biologically degradable polymer, and a liquid, biologically degradable oligomer is placed in the organism and coagulated under the influence of the body fluid.

The invention is explained by the following examples.

Synthesis of Biodegradable, Liquid Oligomers (Examples 1 and 2)

Example 1

Ethyl Ester Oligo-D, L-lactide of L-(-)-Lactic Acid

Under flowing nitrogen, a mixture of 15.0 g (104 mmoles) of D,L-lactide, 12.294 g (104 mmoles) of ethyl of L-(-)-lactate, as well as 2 drops of tin(II) 2-ethyl hexanoate is heated with stirring for 4 hours at 140°C. After the melt is cooled to room temperature, the reaction mixture is dissolved in 40 mL of methylene chloride. This solution is added dropwise to 400 mL of heptane. The product separates out as a viscous oil. The heptane phase of lower density is removed and the solvent residues, remaining in the product, are removed under reduced pressure. Subsequently, the product is dried to constant weight under vacuum. A viscous, colorless oil is obtained.

Yield: 16.02 g

M_n (VPO): 354 g/mole

Example 2

Ethyl Ester Oligo-L-lactide of L-(-)-Lactic Acid

(Starting material 2)

Under flowing nitrogen, a mixture of 15.0 g (104 mmoles) of L-lactide, 12.294 g (104 mmoles) of ethyl L-(-)lactate, as well as 2 drops of tin(II) 2-ethyl hexanoate is heated with stirring for 4 hours at 140°C. After the melt is cooled to room temperature, the reaction mixture is dissolved in 40 mL of methylene chloride. This solution is added dropwise to 400 mL of heptane. The product separates out as a viscous oil. The heptane phase of lower density is removed and the solvent residues, remaining in the product, are removed under reduced pressure. Subsequently, the product is dried to constant weight under vacuum. A viscous, colorless oil is obtained.

Yield: 19.22 g

M_n (VPO): 362 g/mole

Synthesis of Biodegradable Polymers (Examples 3 to 9)

Example 3

(Starting material 3)

Under flowing nitrogen, a mixture of 13.0 g (90.2 mmoles) of D,L-lactide, 0.532 g (4.5 mmoles) of ethyl L-(-)lactate, as well as 2 drops of tin(II) 2-ethyl hexanoate is heated with stirring overnight at 140°C. After the melt is cooled to room temperature, the reaction mixture is dissolved in 40 mL of methylene chloride. This solution is added dropwise to 400 mL of heptane. The product precipitates as a tacky solid. The heptane phase of lower density is subsequently removed. The product is taken up in 40 mL of methylene chloride. After the solvent has been concentrated under reduced pressure, the remaining residues of solvent are removed by drying for several days under vacuum. A glass-like transparent solid is obtained.

Yield: 12.450 g

M_n (GCP, RI): 4346 g/mole

Example 4

(Starting material 4)

Under flowing nitrogen, a mixture of 13.0 g (90.2 mmoles) of D,L-lactide, 0.205 g (1.73 mmoles) of ethyl L-(-)lactate, as well as 2 drops of tin(II) 2-ethyl hexanoate is heated with stirring overnight at 140°C. After the melt is cooled to room temperature, the reaction mixture is dissolved in 40 mL of methylene chloride. This solution is added dropwise to 400 mL of heptane. The product precipitates as a tacky solid. The heptane phase of lower density is subsequently removed. The product is taken up in 40 mL of methylene chloride. After the solvent has been concentrated under reduced pressure, the remaining residues of solvent are removed by drying for several days under vacuum. A glass-like transparent solid is obtained.

Yield: 9.580 g

M_n (GPC, RI): 7790 g/mole

Example 5

(Starting material 5)

Under flowing nitrogen, a mixture of 13.0 g (90.2 mmoles) of D,L-lactide, 1.835 g (4.5 mmoles) of cholesterol, as well as 2 drops of tin(II) 2-ethyl hexanoate is heated with stirring overnight at 140°C. After the melt is cooled to room temperature, the reaction mixture is dissolved in 40 mL of methylene chloride. This solution is added dropwise to 400 mL of heptane. The product precipitates as a tacky solid. The heptane phase of lower density is subsequently removed. The product is taken up in 40 mL of methylene chloride. After the solvent has been concentrated under reduced pressure, the remaining residues of solvent are removed by drying for several days under vacuum. A glass-like transparent solid is obtained. Yield: 13.905 g

M_n (GPC, RI): 4116 g/mole

Example 6

(Starting material 6)

Under flowing nitrogen, a mixture of 13.0 g (90.2 mmoles) of D,L-lactide, 0.918 g (2.25 mmoles) of cholesterol, as well as 2 drops of tin(II) 2-ethyl hexanoate is heated with stirring overnight at 140°C. After the melt is cooled to room temperature, the reaction mixture is dissolved in 40 mL of methylene chloride. This solution is added dropwise to 400 mL of heptane. The product precipitates as a tacky solid. The heptane phase of lower density is subsequently removed. The product is taken up in 40 mL of methylene chloride. After the solvent has been concentrated under reduced pressure, the remaining residues of solvent are removed by drying for several days under vacuum. A glass-like transparent solid is obtained. Yield: 13.528 g

M_n (GPC, RI): 8682 g/mole

Example 7

(Starting material 7)

Under flowing nitrogen, a mixture of 13.0 g (90.2 mmoles) of D,L-lactide, 0.343 g (4.5 mmoles) of 1,2-dihydroxypropane, as well as 2 drops of tin(II) 2-ethyl hexanoate is heated with stirring overnight at 140°C. After the melt is cooled to room temperature, the reaction mixture is dissolved in 40 mL of methylene chloride. This solution is added dropwise to 400 mL of heptane. The product precipitates as a tacky solid. The heptane phase of lower density is subsequently removed. The product is taken up in 40 mL of methylene chloride. After the solvent has been concentrated under reduced pressure, the remaining residues of solvent are removed by drying for several days under vacuum. A glass-like transparent solid is obtained.

Yield: 12.130 g

M_n (GPC, RI): 3794 g/mole

Example 8

(Starting material 8)

Under flowing nitrogen, a mixture of 13.0 g (90.2 mmoles) of D,L-lactide, 0.171 g (2.25 mmoles) of 1,2-dihydroxypropane, as well as 2 drops of tin(II) 2-ethyl hexanoate is heated with stirring for 4 hours at 140°C. After the melt is cooled to room temperature, the reaction mixture is dissolved in 40 mL of methylene chloride. This solution is added dropwise to 400 mL of heptane. The product precipitates as a tacky solid. The heptane phase of lower density is subsequently removed. The product is taken up in 40 mL of methylene chloride. After the solvent has been concentrated under reduced pressure, the remaining residues of solvent are removed by drying for several days under vacuum. A glass-like transparent solid is obtained.

Yield: 12.680 g

M_n (GPC, RI): 7784 g/mole

Example 9

(Starting material 9)

Under flowing nitrogen, a mixture of 13.0 g (90.2 mmoles) of D,L-lactide, 0.201 g (1.5 mmoles) of 1,1,1-trishydroxymethylpropane, as well as 2 drops of tin(II) 2-ethyl hexanoate is heated with stirring for 4 hours at 140°C. After the melt is cooled to room temperature, the reaction mixture is dissolved in 40 mL of methylene chloride. This solution is added dropwise to 400 mL of heptane. The product precipitates as a tacky solid. The heptane phase of lower density is subsequently removed. The product is taken up in 40 mL of methylene chloride. After the solvent has been concentrated under reduced pressure, the remaining residues of solvent are removed by drying for several days under vacuum. A glass-like transparent solid is obtained.

Yield: 12.12 g

M_n (GPC, RI): 11053 g/mole

Polymer-Oligomer Compositions

Example 10

A mixture of 100 mg of poly-D,L-lactide (Example 5, JP 37) and 900 mg oligomeric ester (Example 1, JP 43) is stirred for 5 minutes at 140°C. A viscous, transparent liquid is formed. When this polymer-oligomeric ester is added dropwise to water, a dimensionally stable coagulate is formed.

Release of Biologically Active Materials

Example 11

The viscous, transparent solution of a mixture (of Example 10) of 100 mg of poly-D,L-lactide (starting material 5 or 6) and 900 mg of oligomer (starting material 1) is mixed with 6 mg of cytochrome C, which becomes suspended in the mixture. The suspension is injected into a membrane in a beaker, which contains 500 mL of isotonic sodium chloride solution. The acceptor medium is stirred and the release of cytochrome C from the coagulate, which is formed in situ, is determined after defined time intervals. The release profile is shown in Figure 1.

The viscous, transparent solution of a mixture (from Example 10) of 100 mg of poly-D,L-lactide (starting material 6) and 900 mg of oligomer (starting material 1) is treated with 6 mg of testosterone or testosterone undecanoate, which becomes suspended in the mixture. The mixture is injected into a membrane in a beaker, which contains 500 mL of isotonic sodium chloride solution. The acceptor medium is stirred and the release of testosterone or testosterone undecanoate C from the coagulate, which is formed in situ, is determined after defined time intervals. The release profile is shown in Figure 2.

Claims

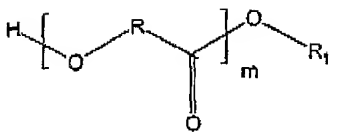
1. An oligomer-polymer composition, consisting of a combination of at least two biologically degradable inert materials and at least one biologically active ingredient.

2. The oligomer-polymer composition of claim 1, wherein the biologically degradable inert materials are polymerization products of identical or different hydroxycarboxylic acids.

3. The oligomer-polymer composition of claim 2, wherein the hydroxycarboxylic acids are lactic acid or glycolic acid.

4. The oligomer-polymer composition of one of the preceding claims, wherein at least one of the biologically degradable inert materials is a liquid, low molecular weight oligomer and the other a solid, higher molecular weight polymer.

5. The oligomer-polymer composition of claim 4, wherein the liquid, low molecular weight oligomer is a compound of the general Formula I, II or III



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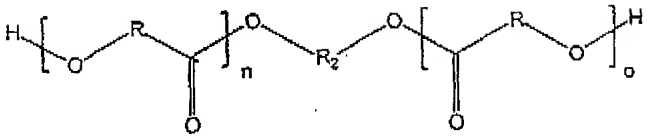
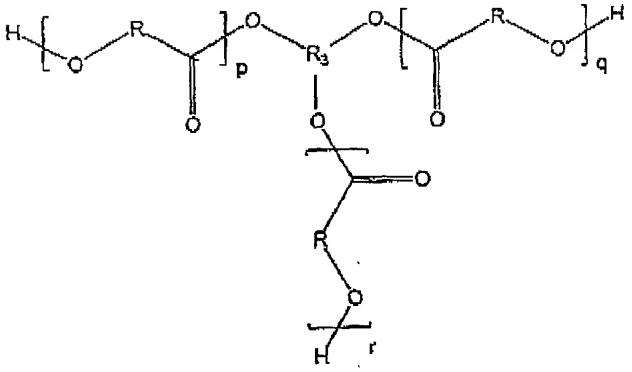


II



II

wherein

R is the same or different for the variables m, n, o, p, q and r and represents $–CH_2-$, $-CH(CH_3)-$, $-(CH_2)_5-$, $–CH_2–CH_2-O–CH_2-$, $–CH_2–CH_2-O–CH_2-CH_2-0-CH_2-$ or their homologs with in each case up to 5 further carbon atoms,

R_1 represents $–CH_2-COOY$, $-CH(CH_3)-COOY$, $-CH_2-CH_2-COOY$, $-CH_2-$ CH_2-CH_2-COOY, $-CH_2-CH_2-CH_2-CH_2-COOY$, $-CH_2-CH_2-CH_2-CH_2-CH_2-COOY$, $-CH_2-CH(CH_3)-Y$, $-(cyclo-C_6H_{11})$ or $-CH_2-C_6H_5$,

R_2 represents $-CH_2-CH(CH_3)-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-CH_2-$, $-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$, $-CH_2-CH(-Y)-CH_2-$, cyclohexane-1,2-diyl, cyclohexane-1,3-diyl or cyclohexane-1,4-diyl,

R_3 represents $(-CH_2)_2CH-$, $(-CH_2)_3-CH_3$ or $(-CH_2)_3C-CH_2-CH_3$,

Y being –H, $-CH_3$, C_2H_5, $-C_3H_7$ or $-C_4H_9$ and

m, n, o, p, q and r independently of one another being a whole number from 2 to 18.

6. The oligomer-polymer composition of claim 5, wherein R is $-CH(CH_3)-$, R_1 is $-CH(CH_3)-COOY$, Y is $-C_2H_5$ and m, n, o, p, q or r is a whole number from 2 to 4.

7. The oligomer-polymer composition of claim 4, wherein the liquid low molecular weight oligomer is selected from the following group or from mixtures of this group, namely poly(hydroxyesters), such as poly-(L-lactides), poly-(D,L-lactides), polyglycolides, poly-(caprolactones), poly(dioxanones), poly-(hydroxybutyric acids), poly-(hydroxyvaleric acids), poly-(glycosalicylates) and copolymers of these compounds, poly-(hydroxy esters), which are synthesized by a ring opening polymerization of lactones in the presence of a biocompatible starter molecule, namely, L-lactide, D,L-lactide, glycolide, p-dioxanone and e-caprolactone, with aliphatic or cycloaliphatic compounds with one or more free hydroxyl groups, such as alkyl L-lactate, cholesterol, 1,2-dihydroxypropane, triethylene glycol, glycerol or pentaerythritol as biocompatible starter molecules.

8. The oligomer-polymer composition of one of the claims 4 to 7, wherein the ratio of solid, higher molecular weight polymer to liquid, lower molecular weight oligomer is 1 : 100 to 1 : 1 and preferably 1 : 10 to 1 : 2.

9. The oligomer-polymer composition of one of the preceding claims, wherein the biologically active ingredient is selected from the group comprising hormones, immune modulators, immune suppressive agents, antibiotics, cytostatic agents, diuretics, gastrointestinal drugs, cardiovascular drugs and neuropharmacological drugs.

10. The oligomer-polymer composition of claim 9, wherein the biologically active ingredient is present in the composition of inactive ingredient in dissolved or suspended form.

11. The oligomer-polymer composition of one of the preceding claims, wherein this composition is present in the form of an injectable material, which, when injected, forms a coagulate under the influence of body fluid.

12. An injectable implant, obtainable by injecting an oligomer-polymer composition of claim 1 into a body.

13. A method for preparing an injectable implant, wherein an oligomer-polymer composition of claim 1 is injected into the body of a mammal.

DECLARATION AND POWER OF ATTORNEY FOR NATIONAL STAGE OF PCT PATENT APPLICATION

As a below-named inventor, I hereby declare that:

Cristoph VOELKEL
Manuela PFEIFFER
Sabine FRICKE
Sebastian VOGT
Ernst-Joachim BORMANN
Matthias SCHNABELRAUCH
Birgitt BEER

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **BIODEGRADABLE, INJECTABLE OLIGOMER-POLYMER COMPOSITION** the specification of which was filed as PCT International Application number PCT/DE 00/00444 on February 11, 2000.

I hereby state that I believe the named inventor or inventors in this Declaration to be the original and first inventor or inventors of the subject matter which is claimed and for which a patent is sought.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365 (b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior foreign application(s):			Priority claimed:	
199 08 753.9	GERMANY	FEBRUARY 20, 1999	X	
(Number)	(Country)	(Date filed)	Yes	No
(Number)	(Country)	(Date filed)	Yes	No

As a named inventor, I hereby appoint the following attorney to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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~~STRIKER, STRIKER & STENBY~~
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~~Huntington, New York 11743~~
U.S.A.

I hereby declare that all statements made herein of my own knowledge are true and that all statements

made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statement may jeopardize the validity of the application or any patent issued thereon.

Signature: X	Date: 24.08.2001	Residence and Full Postal Address: Bibliotheksweg 3 D-07743 Jena Germany DEX
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Signature:	Date:	Residence and Full Postal Address: Theobald-Renner-Strasse 44 D-07747 Jena Germany
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Signature:	Date:	Residence and Full Postal Address: Ibrahimstrasse 3 D-07745 Jena Germany
Full Name of Sixth Inventor: Matthias SCHNABELRAUCH	Citizenship: GERMAN	
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Full Name of Seventh Inventor: Birgitt BEER	Citizenship: GERMAN	

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Full Name of Third Inventor: Sabine FRICKE	Citizenship: GERMAN	
Signature: Sebastian Vogt	Date: 28.08.2001	Residence and Full Postal Address: Ziegenhainer Strasse 67 D-07749 Jena Germany
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Signature: Birgitt Beer	Date: 28.08.01	Residence and Full Postal Address: Dorfstrasse 89 D-07751 Zoellnitz Germany
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